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(74) Agents: **BOETERS, Hans et al.**; Boeters & Lieck, Bere-
iteranger 15, 81541 München (DE).

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(71) Applicant (*for all designated States except US*):
**GESELLSCHAFT FUER BIOTECHNOLOGISCHE
FORSCHUNG MBH (GBF)** [DE/DE]; Mascheroder
Weg 1, 38124 Braunschweig (DE).

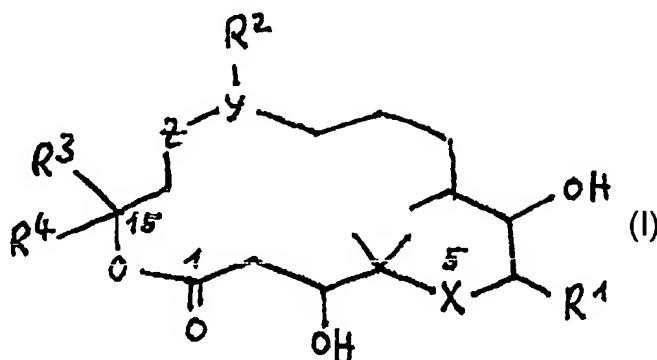
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(72) Inventor; and

(75) Inventor/Applicant (*for US only*): **HOEFLE, Gerhard**
[DE/DE]; Alter Weg 12a, 38124 Braunschweig (DE).

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(54) Title: **GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH (GBF)**



(57) Abstract: The invention relates to 5-thiapethylones and 15-disubstituted epothilones according to formula I (I) with the following meanings: X = >C=O or >S=O R¹ = C₁₋₆ alkyl or C₂₋₆ alkenyl R² = H or C₁₋₆ alkyl Y - Z = >C=C< or >C-O-C< (epoxide ring) R³ = H, C₁₋₆ alkyl or C₂₋₆ alkenyl R⁴ = bicycloaryl, bicycloheteroaryl or -C(R⁵) = CH-R⁶, where R⁵ = H or CH₃ and R⁶ = aryl or heteroaryl X not being >C=O if R³ = H.

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Gesellschaft für Biotechnologische Forschung mbH (GBF)

5-THIAEPOTHILONES AND 15-DISUBSTITUTED EPOTHILONES

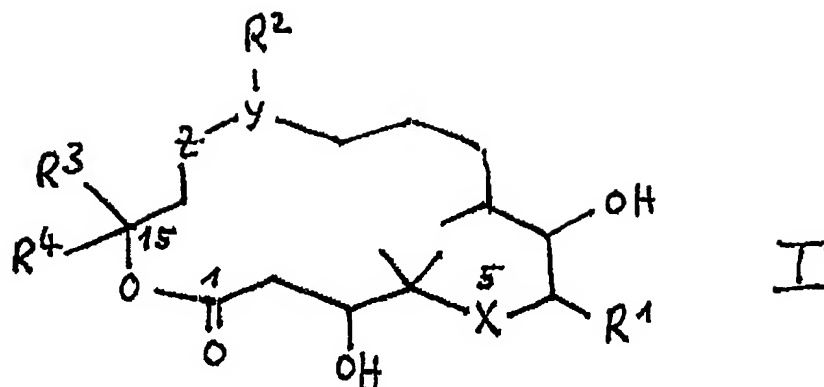
The present invention relates to 5-thiaepothilones and 15-disubstituted epothilones which are 16-membered cytotoxic macrolides of formula I with an application potential in cancer therapy and in the treatment of other instances of cell growth impairment.

Epothilones are well known. They can be obtained by fermenting the myxobacterium *Sorangium cellulosum* (GBF) by semisynthesis (GBF, BMS) by genetic engineering and heterologous expression (Kosan Biosciences), by total synthesis (Danishefsky, Nicolaou, Schinzer, Novartis, Schering).

All the epothilones which have become known so far have the common characteristic of carrying a keto group ($X = \text{carbonyl}$) in position 5 and a hydrogen ($R^3 = H$) on the C15 atom. The present invention relates to epothilones which, in contrast to the known state of the art, exhibit either

- (1) a sulphoxide group for X or
- (2) an alkyl or alkenyl group by way of R^3 on the C15 carbon atom or
- (3) both a sulphoxide group X and an alkyl or alkenyl group as radical R^3 .

The invention also relates to epothilones of the following general formula I:



with the following meanings:

$$X = >C = 0 \text{ or } >S = 0$$

$R^1 = C_{1-6}$ alkyl or C_{2-6} alkenyl

$$R^2 = \text{H or } C_{1-6} \text{ alkyl}$$
$$Y - Z = >C=C< \text{ or } >C-O-C< \text{ (epoxide ring)}$$
$$R^3 = H, C_{1-6} \text{ alkyl or } C_{2-6} \text{ alkenyl}$$
$$R^4 = \text{bicycloaryl, bicycloheteroaryl or } -C(R^5) = CH-R^6,$$

where

$$R^5 = H \text{ or } CH_3 \text{ and}$$

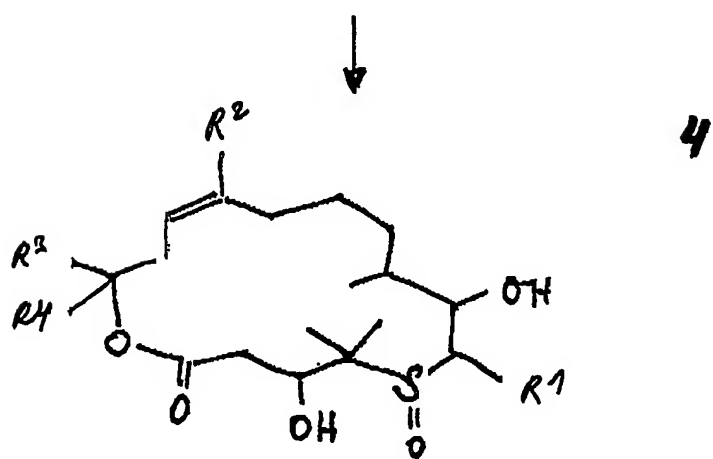
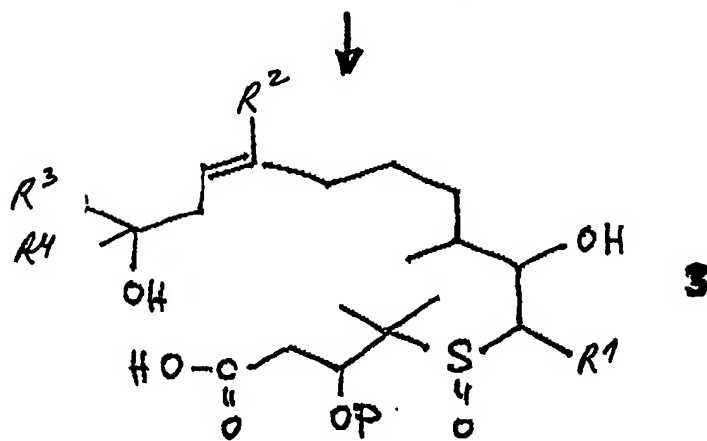
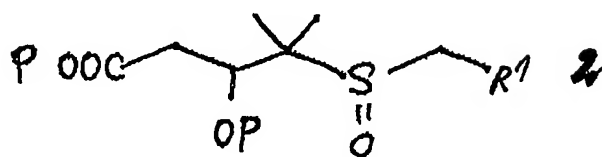
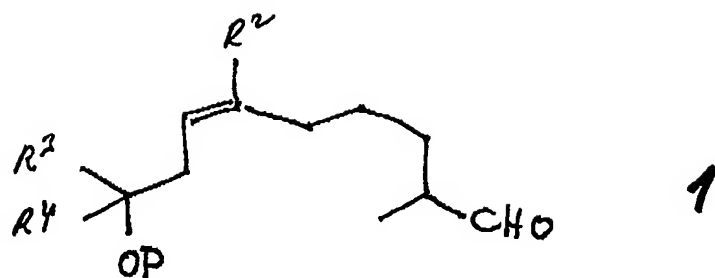
R^6 = aryl or heteroaryl

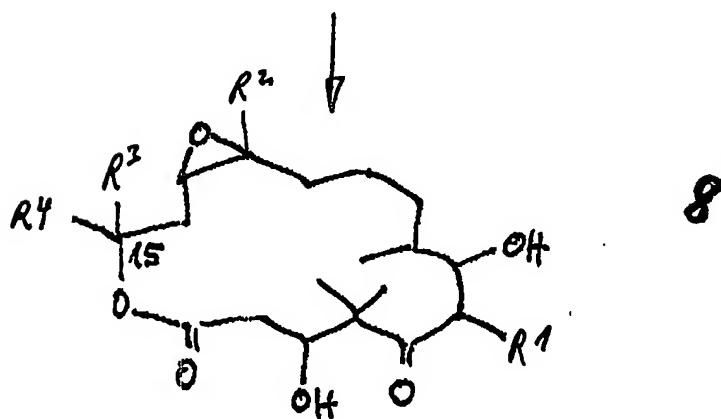
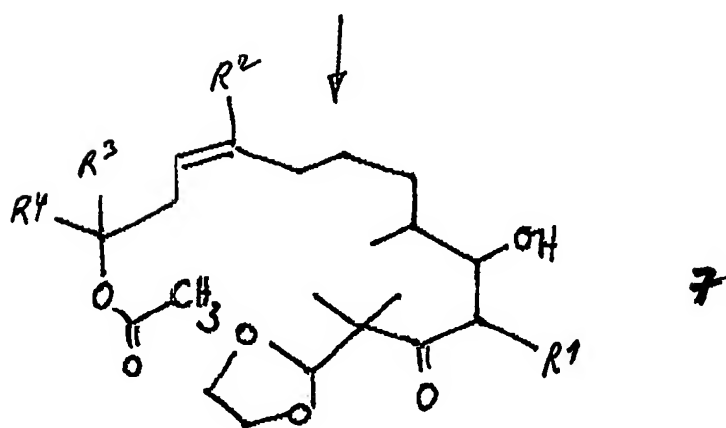
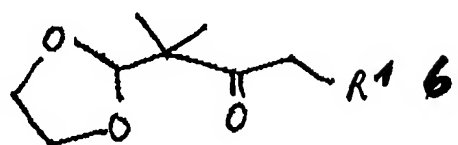
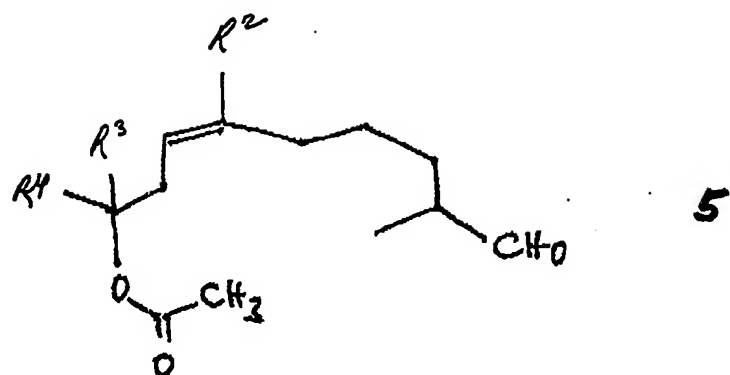
X not being $>C=O$ if $R^3 = H$.

A compound of the general formula I with $Z-Y = >C=C<$ can be produced from a compound of formula 1 by aldol reaction with a compound of formula 2. In the following reaction scheme, P represents a protective group common in epothilone chemistry, such as a silyl group. Subsequently, the compound of formula 3 thus obtained is reacted, with ring closure (formation of lactone), to a compound of formula 4.

A compound of the general formula I with $Y-Z = >\underline{C-O-C}<$ (epoxide ring) can be produced by reacting a compound of formula 5 with a compound of formula 6 in an aldol

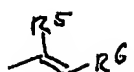
reaction. The resulting compound of formula 7 can be cyclised after liberating the aldehyde group from the acetal in an aldol reaction, whereupon the lactone thus obtained is subjected to epoxidation in position 12,13.



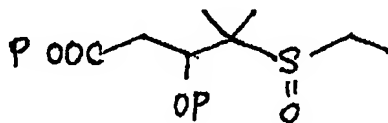
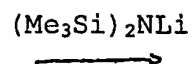
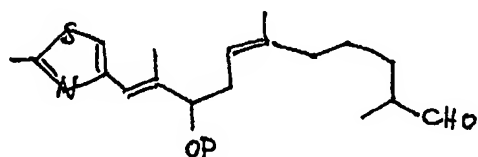


Below, the invention is further illustrated by two synthesis examples.

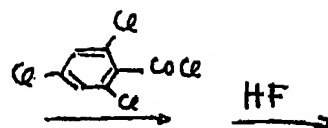
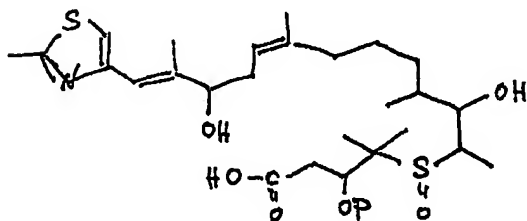
Synthesis example Ia: $X = SO$, $R^1, R^2 = CH_3$,

$Z - Y = C=C$, $R^3 = H$, $R^4 =$ 

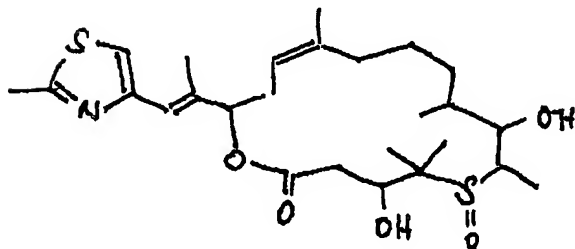
with $R^5 = CH_3$, $R^6 = 4-(2\text{-methylthiazolyl})$



P = protective groups, e.g. silyl

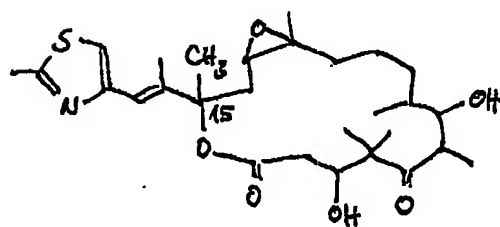
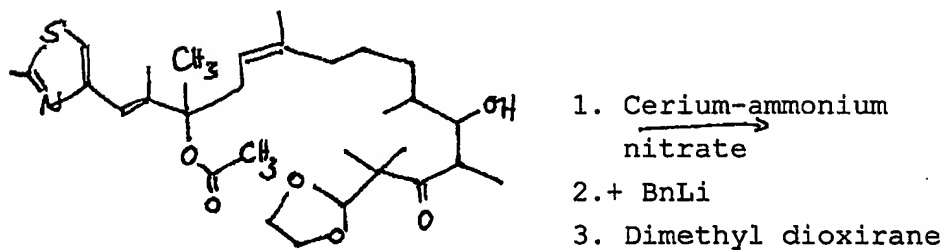
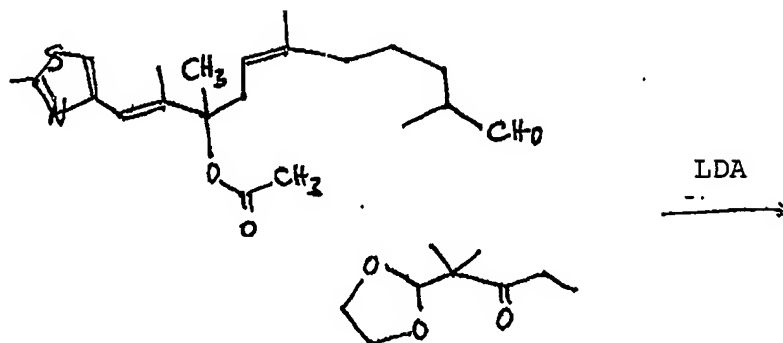
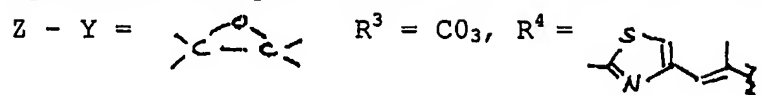


Net_3 , DMAP, pyridine



5-thiaepothilone

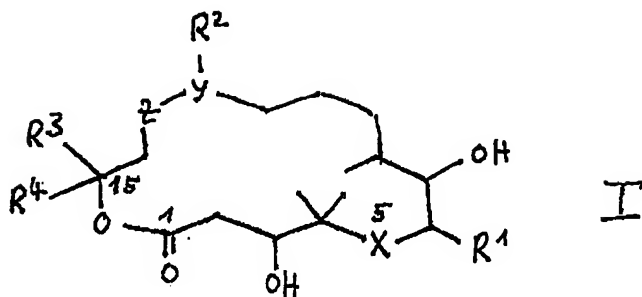
Synthesis example Ib: $X = C = O$, $R^1, R^2 = CH_3$,



= 15-Methyl epothilone B

CLAIMS

1. Epothilone of the general formula (I):



with the following meanings:

X = >C = O or >S = O and/or

R¹ = C₁₋₆ alkyl or C₂₋₆ alkenyl and/or

R² = H or C₁₋₆ alkyl and/or

Y - Z = >C=C< or >C-O-C< (epoxide ring) and/or

R³ = H, C₁₋₆ alkyl or C₂₋₆ alkenyl and/or

R⁴ = bicycloaryl, bicycloheteroaryl or -C(R⁵) = CH-R⁶,

where

R⁵ = H or CH₃ and

R⁶ = aryl or heteroaryl,

X not being >C=O if R³ = H,

and one, a plurality or all conceivable combinations of the radicals X, R¹, R², R³, R⁴, R⁵, R⁶ and Y - Z

2. Epothilone according to claim 1, where R⁴ is a bicycloaryl or bicycloheteroaryl radical common in epothilone chemistry.
3. Epothilone according to claim 1, where R⁶ is an aryl or heteroaryl radical common in epothilone chemistry.

4. Epothilone according to claim 3, where the heteroaryl radical is a monocyclic 5 or 6-membered heteroaromatic which may exhibit one or a plurality of O and/or N and/or S atoms in the ring.
5. Epothilone according to claim 3, where the aryl radical may be a heteroaromatic with one or a plurality of and in particular 1, 2, 3 or 4 heteroatoms.
6. Agent for cancer therapy and/or treating other instances of cell growth impairment, consisting of or containing one or a plurality of epothilones according to any one of the preceding claims, apart from the usual auxiliary agents.

INTERNATIONAL SEARCH REPORT

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According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used) CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 02514 A (BRISTOL-MYERS) 21 January 1999 (1999-01-21) page 64; claims 1,3-5	1,3,6
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
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International Application No
PCT/EP 03/06066

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9902514	A	21-01-1999	AU 731497 B2	29-03-2001
			AU 7972098 A	08-02-1999
			BG 104068 A	29-09-2000
			BR 9810555 A	15-08-2000
			CN 1270589 T	18-10-2000
			EE 200000013 A	15-08-2000
			EP 1019389 A2	19-07-2000
			HU 0103111 A2	29-04-2002
			JP 2002512634 T	23-04-2002
			LT 99153 A , B	25-08-2000
			LV 12569 A	20-11-2000
			LV 12569 B	20-04-2001
			NO 20000076 A	07-01-2000
			NZ 501198 A	28-09-2001
			PL 338003 A1	25-09-2000
			SK 181799 A3	06-08-2001
			TR 200000065 T2	21-11-2000
			US 6605599 B1	12-08-2003
			WO 9902514 A2	21-01-1999
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